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| 10/538,245 | 06/07/2005 | David Feifel | 00015-067US1/SD2003-090-1 | 3580 |

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| EXAMINER | |
|---|---|
| DUTT, ADITI | |

| ART UNIT | PAPER NUMBER |
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| 1649 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/538,245 | FEIFEL, DAVID | |
| | Examiner | Art Unit | |
| | Aditi Dutt | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15-18,22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18,22 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application, Amendments and/or Claims*

1. The amendments filed on 27 April 2010 have been entered into the record and have been fully considered.

2. Claims 15-18, 22, and 24-26, drawn to a method for increasing sensorimotor gating or inhibiting serotonin-2A and/or alpha-1 receptor mediated neural function by administration of neurotensin agonist to a human subject, are being considered for examination in the instant application.

### *Response to Amendment*

Declaration under 37 C.F.R. § 1.132

3. The declaration submitted by Dr. David Feifel dated 27 April 2010 is acknowledged and considered in full.

Priority

4. Applicant argues that the provisional application filed in 2002 contemplates neurotensin mimetics and discloses NT69L on pages 4-6 of the said document.

5. Applicant's argument has been considered, however, not found to be persuasive. Although the provisional application generally suggests that

neurotensin agonists "may inhibit 5-HT2A transmission" (page 2, abstract), pages 4-6 describe the effect of only one NT agonist PD149163, that was potent in reversing prepulse inhibition (PPI) and the effects of the serotonin receptor (5-HT2A) agonist (1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride) or DOI.

6. It is however, noted that the '937 provisional application does not disclose the invention of independent claims 15, 16, 17, 18, 22, 24-26. With respect to the independent claims, there is simply no disclosure of the specifically listed NT agonists, with the exception of PD149163. For example, there is no disclosure of (Boc-Lys9)-neurotenin(9-13)-methyl ester, or of (Dab9)-neurotensin(8-13), or of (lys9 Trp11, Glu12)-neurotensin(8-13), or of NT1, or of NT2, and so on. Furthermore there is no disclosure of the compounds listed in claim 17, the routes of administration in claim 18. There is no disclosure of administration to human patients with the specific diseases recited in the independent claims.

7. Furthermore, although Applicant had conceived of trying NT69L in the provisional application, the provisional application (page 8 para 3) shows that NT69L and NT8-13 were NOT effective in reversing the effects of DOI (see Events relevant to Invention, page 2, para 2, 3). Therefore, Applicants were not in possession of the invention now claimed, which includes administering NT69L to human patients with bipolar disease, anxiety disease, or depression associated w 5-HT2A mediated neurotransmission. In other words, the disclosure

of the '937 provisional application does not enable the use of NT69L for reversing the effects of DOI.

Withdrawn objections and/or rejections

8. Upon consideration of the declaration dated 4/27/2010, stating that the conception described in the Shilling reference is Dr. Feifel's, and that the other authors of the reference are not inventors of the present application and only worked under David Feifel's supervision, the rejection of claims under 103(a) using the Shilling reference as the primary reference is withdrawn.

***New Rejections***

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 15-16, 18, 22, and 24 and 26 under 35 U.S.C. 103(a) as being unpatentable over Wettstein et al., (Prog Neuropsychopharm Biol Psychiat 23: 533-544, 1999) and Vollenweider et al (Neurorep 9: 3897-3902, 1998); in view of

Bowden (Psychiat Serv 52: 51-55, 2001); and further in view of Perry et al. (Biol Psychiat 50: 418-424, 2001).

10. The claims are drawn to a method for increasing sensorimotor gating or inhibiting serotonin-2A and/or alpha-1 receptor mediated neural function in a human subject having a bipolar disease or disorder, anxiety disease or disorder depression disease or disorder, comprising the administration of a neurotensin (NT) agonist, alone or in combination with other psychotropic drugs, to improve symptoms of the disorder (claims 15-16, 22, 24). The claims further recite that the administration of NT agonist is via various routes such as parenteral, topical, subcutaneous, etc. (claims 18 and 26). Please note that a disorder is generally interpreted as an abnormality of function, while a disease is an illness with a recognizable set of symptoms and signs, thereby making a disorder broader than a disease.

11. Wettstein et al teach the selectivity of action of atypical antipsychotic drugs (e.g. NT agonists or NT1) as antagonists of the behavioral effects produced by the psychotropic serotonin receptor agonist DOI following intraperitoneal (i.p.) administration of DOI and NT1 in rats. The reference teaches that NT1 antagonizes and attenuates the behavioral effects of DOI like head and body shakes, fore paw tapping, skin jerks etc., in a dose dependent manner (page 536, para 2; figure 4; abstract; page 540, para 1). Since DOI is a hallucinogen producing a clinical state similar to psychosis of schizophrenia, DOI is a psychoactive compound (page 539, para 2). Because DOI is a serotonin

receptor agonist and because NT1 administration antagonizes the antipsychotic effect of DOI, NT1 inhibits serotonin-2A mediated neurotransmission.

12. Wettstein et al. do not explicitly state the association of PPI deficits and 5-HT2A transmission. Wettstein et al. also do not teach the administration of NT1 in a human subject and the association of psychosis with bipolar disorder, anxiety or depression.

13. Vollenweider et al teach that psychotic disorders have the 5-HT2A receptor changes and PPI deficits, and that serotonergic hyperactivity results in such disorders. The reference also teaches that the 5-HT2A agonist DOI disrupts the PPI in rats (page 3901, col 2, para 1).

14. Bowden teaches that bipolar disorder, depression disorder, anxiety disorders and schizophrenia are overlapping disorders in humans that have psychosis as a common feature (page 54, col 2, para 1; col 3).

15. Perry et al. teach that sensorimotor gating deficits as assessed by significantly lower PPI and habituation of the human startle response is observed in bipolar disorder patients (Abstract).

16. It would have therefore, been obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the use of NT1 for reversing the effects of DOI induced psychotic behavior and PPI deficits in rats as taught by Wettstein et al., and Vollenweider et al. by administering NT1 to a bipolar disorder human subject to increase PPI and thereby increase sensorimotor gating in view of Bowden and Perry et al. The person of ordinary

skill in the art would have been motivated to use the NT agonist NT1 in human subjects as this compound can reverse all effects of DOI and therefore, prove to be an atypical antipsychotic (by reversing serotonin-2A transmission) in clinical development (Wettstein et al. page 540, para 1). The person of ordinary skill in the art would have also been motivated to use serotonin-2A transmission inhibitors because typical antipsychotic agents (primarily reversing dopamine neurotransmission) are known to result in debilitating side-effects like motor control disabilities. Therefore, as Wettstein et al. indicate "research emphasis has been placed on discovering drugs that better treat the disease while having side-effect profiles much improved over the conventional compounds" (page 534, para 1). The person of ordinary skill in the art would have expected success as the development of atypical antipsychotics antagonizing the serotoninergic transmission for obtaining increased efficacy with decreased side effects was a continuing effort in the medical and pharmaceutical community at the time the invention was made.

17. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

18. Claims 15-18, 22, and 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wettstein et al., (1999), Vollenweider et al (1998), Bowden (2001) and Perry et al. (2001), in view of Greibel et al. (Neurosc Behav Rev 25:

619-626, 2001).

19. Claims 17 and 25 further teach the administration of a compound selected from the group consisting of levocobastine, SR48692 and SR142948.

20. The teachings of Wettstein et al., Vollenweider et al, Bowden and Perry et al. are set forth above.

21. Wettstein et al., Vollenweider et al. Bowden or Perry et al. do not teach further administration of a compound selected from levocobastine, SR48692 and SR142948.

22. Griebel et al teach that intraperitoneal administration of NT1 receptor antagonist SR48692 in rodent models results in effectively treating generalized anxiety disorders (Figure 4; abstract; page 624, col 2, para 2).

23. Neither the combination of Wettstein et al., Vollenweider et al. Bowden and Perry et al. nor the teachings of Griebel et al. teach a process for increasing sensorimotor gating in a subject having the claimed disorders by administration of NT1 or NT1 plus psychotropic drug (DOI) and another compound, SR48692. However, in the absence of unexpected results, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of the references and to administer NT1 or NT1 plus DOI along with SR48692. Each of the compounds, NT1 and the NT receptor antagonist SR48692 had been taught by the prior art to behave as antipsychotic compounds. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two

compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, given the teaching of the prior art of processes using the administration of NT1 or SR48692 individually for increasing sensorimotor gating in psychiatric disorders like bipolar disorder or anxiety, thereby implicating an usefulness in neuropsychiatric conditions, it would have been obvious to administer to a subject both NT1 and SR489692, because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as antipsychotic compounds for the same purpose of in neuropsychiatric diseases, for example as in the claimed invention. One of ordinary skill in the art would have reasonably expected to obtain the claimed effect of increasing sensorimotor gating upon administration of either or both of these neurotensinergic compounds since both had been implicated for clinical usefulness in neuropsychiatric disorders in the prior art.

24. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

***Conclusion***

25. No claims are allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is 571-272-9037. The examiner can normally be reached on M-F.

27. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

28. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
12 July 2010

/Jeffrey Stucker/
Supervisory Patent Examiner, Art Unit 1649